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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,190	01/26/2004	Pnina Fishman	FISHMAN=9B	6424

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EXAMINER

HOWARD, ZACHARY C

ART UNIT PAPER NUMBER

1646

DATE MAILED: 04/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/763,190

Applicant(s)

FISHMAN ET AL.

Examiner

Zachary C. Howard

Art Unit

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 13 January 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-17 and 25-31 is/are pending in the application.
- 4a) Of the above claim(s) 3-6, 11, 13-15 and 26-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1, 2, 7-10, 12, 16, 17, 25, 30 and 31 is/are rejected.
- 7) ☒ Claim(s) 1, 2, 7-10, 12, 16, 17, 25, 30 and 31 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 January 2004 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>9/14/2004</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. Applicant's amendments filed 1/13/2005 are acknowledged. Claims 18-24 have been canceled. Claims 1-7, 12-17 and 25-31 have been amended. Claims 1-17 and 25-31 are pending.

#### ***Election/Restrictions***

2. Applicant's election without traverse of Group I, claims 1-17 and 25-31, in the reply filed on 1/13/2005 is acknowledged. The remaining claims (18-24), which were placed in Group II, have been canceled by Applicant as indicated above.

Three species elections were required. Applicant's election of the following species is acknowledged:

1) The elected species of biological marker is the A3 adenosine receptor (A3AR). The examiner indicated in the Restriction Requirement that no claims were generic with regard to the biological marker. Applicant argues in the reply 1/13/2005 that claim 1 with regard to the species of biological marker. Applicant further indicates that the following claims read on the elected biological marker: 1, 2, 7-17, 25, 30 and 31. The examiner agrees on both points.

Claims 3-6 and 26-29 are drawn to species of biological markers other than A3AR. Claims 3-6 and 26-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

2) The elected species of physiological parameter is the level of protein expression.

3) The elected species of specific disease state is cancer, specifically colon carcinoma.

Claims 11 and 13-15 are drawn to species of disease states other than cancer. Claims 11 and 13-15 are withdrawn from further consideration pursuant to 37 CFR

Art Unit: 1646

1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2, 7-10, 12, 16, 17, 25, 30 and 31, in so far as they are drawn to the elected species, are under consideration.

### ***Information Disclosure Statement***

Reference AA of the Information Disclosure Statement filed 9/14/2004 by Applicant is listed as US 2002/115635 A1, Publication Date 08-22-2002, Applicant Pnina Fishman et al has been lined through because the incorrect publication number was listed. The correct number is U.S. Publication 2002/0115635. This reference has been fully considered and has been listed on the Notice of Reference Cited (PTO-892) included with this Office Action.

### ***Drawings***

Figure 10 of the drawings is objected to under 37 CFR 1.83(a) because it fails to show the detection of the A3AR receptor on human neutrophils as described in the Brief Description of the Drawings on page 20 of the specification. Specifically, all of the lanes (1-3) for all of the samples (1 and 2) are blank; they do not show anything. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and

informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

### ***Specification***

The disclosure is objected to because of the following informalities:

1) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title "Diagnostic markers for therapeutic treatment" is not descriptive because it is too vague.

2) Page 37, line 3 refers to a Figure 4C of the specification. However, Figure 4 only has parts A and B, and the Brief Description of the Figures on page 18 describes only parts A and B of Figure 4.

3) It is not clear what is shown in Figure 5a and 5b. In the Brief Description of the Figures on pages 18-19, Figure 5a and 5b are indicated to "... show the correlation in tumor size and the level of regulatory elements in colon carcinoma cells, wherein Figure 5a presents tumor size after 15 days of daily treatment with IB-MECA of mice inoculated with B16 melanoma cells..." (emphasis added). This statement appears contradictory because according the details provided on pages 30 and 31, in vivo studies were performed either with B6-F10 murine melanoma cells or with HCT-116 human colon carcinoma cells. Furthermore, Example 3 states that Figures 5a and 5b show suppression of B16-F10 melanoma tumor growth and Western blot analysis of this tumor, whereas Example 4 in apparent contradiction states that Figure 5a and 5b show 116 human colon carcinoma cell growth and Western blot analysis of this tumor.

4) In example 10, paragraph 92, it is indicated that the neutrophil cells are incubated with the A3AR agonist CF101 for 15 minutes. Paragraph 93 indicates that the results of the experiment are shown in Figure 10. However, both Paragraph 93 and Figure 10 indicate that the cells were incubated with the A3AR agonist IB-MECA. Due to this apparent contradiction it is not clear which antagonist was actually used.

5) In example 11, paragraph 94, MRS 1220 is incorrectly referred to as an A3AR agonist ("...the specific A3AR agonist MRS 1220..."). MRS 1220 is an A3AR antagonist, as correctly described in paragraph 95 ("...the A3AR antagonist MRS 1220.")

Appropriate correction is required.

### ***Claim Objections***

Claims 1, 2, 7-10, 12, 16, 17, 25, 30 and 31 are objected to because the claims encompass non-elected species.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 7-10, 12, 16, 17, 25, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of monitoring the effectiveness of an agent that interacts with an A3AR receptor in the treatment of colon carcinoma or melanoma by measuring the protein expression of A3AR, PKA, PKB/Akt, GSK-3 $\beta$ ,  $\beta$ -catenin, cyclin D1, c-myc, or NF- $\kappa$  $\beta$ , or the treatment of adjuvant-induced inflammation by measuring the protein expression of A3AR, PI3K, PKB/Akt, IKK, TNF-alpha, GSK-3B or caspase-3, does not reasonably provide enablement for 1) a method of monitoring the effectiveness of in treatment of the aforementioned diseases by measuring other parameters (mRNA, localization, or phosphorylation), or for any other diseases by any parameter, 2) for a method for determining whether a drug candidate is an A3AR agonist useful in treating a disease state, or 3) for a method wherein the parameter is measured at a time point wherein the differences "are expected to be most prominent". The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of monitoring the effectiveness of an agent that interacts with the A3 adenosine receptor (A3AR) after administration to an individual with a disease. This method comprises withdrawing a sample of cells associated with a disease subsequent to treatment with an agent that interacts with A3AR, detecting the level of one parameter of A3AR or an element associated with a transduction pathway downstream of A3AR, comparing the level to the level prior to administration of an agent or to the level in an untreated individual, and concluding that a difference in the level is indicative of the effectiveness of said treatment against the disease.

To practice the invention as claimed, one of skill in the art would need know that correlation exists between the difference in the measured level of the marker and effective in vivo treatment of the disease state.

The Applicants have correlated inhibition of in vivo tumor growth with a change in the level of markers for the following:

IB-MECA suppressed the growth of B16-F10 melanoma and HCT-116 human colon carcinoma in mice inoculated with these tumor cells (Examples 3, 4, and 8). Applicant has correlated this inhibition of growth with a decrease in protein expression of A3AR, PKA, PKB/Akt,  $\beta$ -catenin, cyclin D1, c-myc and NF- $\kappa$ B and an increase in protein expression of GSK-3 $\beta$ .

The Applicants have correlated inhibition of in vivo adjuvant-induced arthritis with a change in the level of markers for the following:

In rats with adjuvant-induced arthritis treated daily with IB-MECA, the anti-inflammatory response induced by IB-MECA is correlated with a down-regulation in the level of protein of A3AR, PI3K, PKB/Akt, IKK, and TNF-alpha and an up-regulation in the level of GSK-3B and caspase-3 (Example 11).

The Applicants have correlated these particular disease states with a change in particular markers in response to IB-MECA. If one had a molecule known to interact with A3AR (a limitation included in claim 1), one of skill in the art could use these markers to determine if the A3AR-interacting molecule was effective in treating the disease correlated with that marker.

The remainder of Applicants' results are from isolated cells in vitro.

Claims 1, 2, 7, 16, and 17 encompass the method practiced with any disease state. The term "disease state" encompasses a vast number of conditions of widely varying etiology including cancer, inflammation, microbial infection, genetic diseases, toxicity caused by chemical compounds, etc. For the vast majority of these diseases, Applicants have not shown that a correlation exists between expression of an A3AR-associated marker and effective in vivo treatment of the disease state with an agent that interacts with an A3AR receptor. It is not predictable whether other diseases would be treatable with A3AR receptor agonists even if expression of the markers would be the same. In order to know that expression of a marker in response to an A3AR-interacting molecule was indicative of effective disease to conclude that said treatment is effective against the disease state, one of skill in art would need to know the correlation between the difference in level of the physiological parameter from control and the effectiveness of said treatment for that disease.

Claim 8 encompasses any "proliferative-related disease", which includes (see paragraph 19 of page 11 of the specification): "all types of cancer; and, in particular, all types of solid tumors; skin proliferative diseases (e.g., psoriasis); a variety of benign hyperplastic disorders; inflammatory diseases; and others." Claim 9 encompasses any type of cancer. Claim 10 encompasses melanoma, colon carcinoma, and prostate



Art Unit: 1646

cancer. While applicant has correlated effective treatment of melanoma and colon carcinoma with expression of A3AR-associated molecules, it is not predictable that for other forms of cancer whether or not the expression of A3AR-associated molecules will be correlated with effective treatment of that particular form of cancer.

All of the claims encompass determining effective treatment by measuring the level of a marker by measuring any of the following parameters: protein expression, mRNA expression, phosphorylation, or cellular localization. However, Applicants have only correlated protein expression with effective in vivo treatment. It is not predictable that the other parameters will be correlated with the effective treatment. For example, a change in protein expression can be due to a change in transcription, translation, or the rate of degradation of the protein. Therefore, the level of mRNA may not change despite a change in the level of protein. To use the level of mRNA to determine if a treatment is effective, one of skill in the art would need to measure the in vivo level of mRNA in individuals in which treatment is effective.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification how the method of the present invention could be used to determine the effectiveness of treatments with other diseases, or by parameters other than protein expression. There are no examples of using the method to determining that an A3AR-interacting agent is effective in treatment of a disease in which a correlation between expression and treatment has not been established, or by using parameters other than protein expression. Thus the specification fails to teach the skilled artisan how to use the method to gauge effectiveness of an agent in treatment without resorting to undue experimentation to determine whether or not such a correlation exists. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if the method could be used diagnostically for any disease, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the

teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

With respect to claims 25, 30, and 31, these claims lack enablement because the method steps do not enable one to identify whether a drug candidate is an A3AR agonist useful in treating a disease state. These claims are drawn to a method for determining whether a drug candidate is an A3AR agonist useful in treating a disease state by administering said drug candidate, withdrawing a cell sample after time, measuring a parameter of A3AR or an element associated with a signaling pathway downstream of A3AR, comparing the level of the parameter to the level in an untreated diseased individual, and if there is a difference concluding that the drug candidate is an A3AR agonist. Applicant has shown that agonists of the A3AR receptor down-regulate A3AR expression, and also inhibit members of the Wnt pathway, resulting in changes in expression of proteins. However, drug candidates could cause these effects through mechanisms other than by agonizing A3AR. For instance, the frizzled receptor activates the Wnt pathway. An antagonist of frizzled could cause down-regulation of members of this pathway. Furthermore, drug candidates could directly decrease the transcription or translation, or increase the rate of degradation, of A3AR or a member of the Wnt pathway, without being an A3AR agonist. In order to practice the claimed invention, one of ordinary skill in the art would need to engage in further experimentation to determine whether or not the drug candidate is or is not an A3AR agonist. Furthermore, claim 25 does not indicate whether an increase or a decrease in the level of the parameter between treated and untreated individuals is indicative of an A3AR agonist, and based on the limited examples provide by Applicant, it is likely that most of the parameters of the markers would only indicate an agonist if either an increase or a decrease was noted.

With respect to claim 16, the claim introduces a limitation that the parameter is measured at a time point wherein the differences "are expected to be most prominent". Claim 16 is broadly drawn to encompass any of the envisioned parameters (protein or mRNA expression, phosphorylation, localization) with of the aforementioned markers. However, the specification does not indicate, for any of these parameters, or markers,

Art Unit: 1646

when the difference are expected to be most prominent between the treated and untreated individuals. The specification also does not indicate whether or not the time point where the difference is most prominent is correlated with effective in vivo treatment. As is noted above, for a number of the parameters (mRNA expression, phosphorylation, localization), no correlation has been established between a difference in the parameter between treated and untreated individuals and in vivo effective treatment. Due to the large number of parameters and markers, it would be undue experimentation for one of ordinary skill in the art to determine the time point of most prominent difference and determine whether or not this is correlated with effective in vivo treatment.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 2, 7-10, 12, 16, 17, 25, 30 and 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear how a difference in the level of the physiological parameter is indicative of the effectiveness of said treatment. It is not clear what kind of a difference (increase or decrease) indicates that the treatment is effective or ineffective.

Claim 25 is indefinite because it is unclear how a difference in the level of the physiological parameter is indicative of an agonist of A3AR. It is not clear what kind of a difference (increase or decrease) indicates that the drug candidate is an A3AR agonist.

Claims 2, 7-10, 12, 16, 17, 25, 30 and 31 are also rejected for depending from rejected claim 1 or rejected claim 25.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 7-10, 12, 17, 25, 30 and 31 are rejected under 35 U.S.C. 102(a) and 102 (e) as being anticipated by Fishman et al, US Pub. No. 2002/0115635, published 8/22/2002 and filed 2/21/2001.

It is noted that, while the inventive entities of the claimed invention and the reference share a common inventor, the inventive entity of Fishman et al, US Pub. No. 2002/0115635 differs from the inventive entity of the claimed invention of the instant application and therefore, the reference is deemed to be within the scope of the statute ("by others . . . before the invention thereof by applicant for a patent.").

In the instant application, the independent claims 1 and 25 recite a method comprising the steps of withdrawing a sample of diseased cells (or associated tissue) from a subject following administration of A3AR-interacting agent, detecting the level of A3AR or an element associated with a signaling pathway downstream of A3AR, and comparing the level to an untreated subject, and concluding that a difference (a decrease) in the level of these markers indicates that the agent is effective in treating the disease state (claim 1) or that the agent is an A3AR agonist (claim 25). The dependent claims introduce limitations that the agent is an A3AR agonist (claim 2), specific parameters/markers measured (claims 7, 12, and 30), subgenus and species of disease states (claims 8-10 and 31) or that the agent is IB-MECA (claim 17).

Art Unit: 1646

In Examples 2 and 3 (page 6), Fishman describes a method comprising the following steps: withdrawing a sample of human colon carcinoma cells from mice following administration of CI-IB-MECA (an A3AR agonist), detecting the protein expression level of B-catenin, cyclin D1, and c-myc, comparing the level to untreated mice, and concluding that a difference (a decrease) in the level of these markers indicates that the compound is effective in treating the tumor. This method meets all of the steps of independent claims 1. Because the compound used was an A3AR agonist, and the difference indicates that this compound was an A3AR agonist, this method also meets all of the limitations of claim 25 of the instant application. Furthermore, the specific agent (CI-IB-MECA, an A3AR agonist), the specific parameters/markers (protein expression of  $\beta$ -catenin, cyclin D1 and c-myc) and the disease state (colon carcinoma) of this method meet all of the limitations of the dependent claims 2, 7-10, 12, 30 and 31.

Claim 17 of the instant application recites that the agonist must be IB-MECA. Fishman teaches on page 3 that IB-MECA or CI-IB-MECA may be used as an A3AR agonist, and thus the method of Fishman anticipates all of the limitations of Claim 17.

### ***Art of Note***

The following article was found by the Examiner during the art search and while not relied upon for a rejection is considered pertinent to the instant application:

Fishman et al, 2002. Evidence for involvement of Wnt signaling pathway in IB-MECA mediated suppression of melanoma cells. *Oncogene*. 21: 4060-4064. Fishman discloses that the level of protein expression of members of the Wnt pathway change in response to treatment with IB-MECA in melanoma cells grown in vitro. Fishman does not correlate the change in these markers with effective in vivo treatment of melanoma.

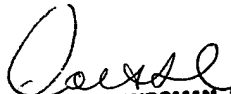
Art Unit: 1646

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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ROBERT S. LANDSMAN, PH.D  
PRIMARY EXAMINER